



Scheme 2

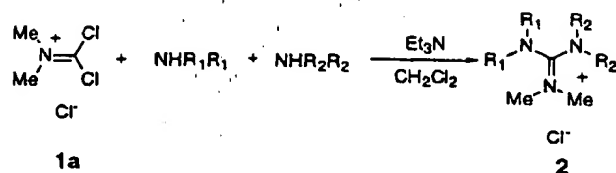


Table 1. Condensation of Secondary Amines on Compound 1a

NHR <sub>1</sub> R <sub>1</sub>	NHR <sub>2</sub> R <sub>2</sub>	compd	yield (%)
NH(Et) <sub>2</sub>	pyrrolidine	2g	100
NH(Bn) <sub>2</sub>	pyrrolidine	2h	88
NH(IPr) <sub>2</sub>	pyrrolidine	2i	76

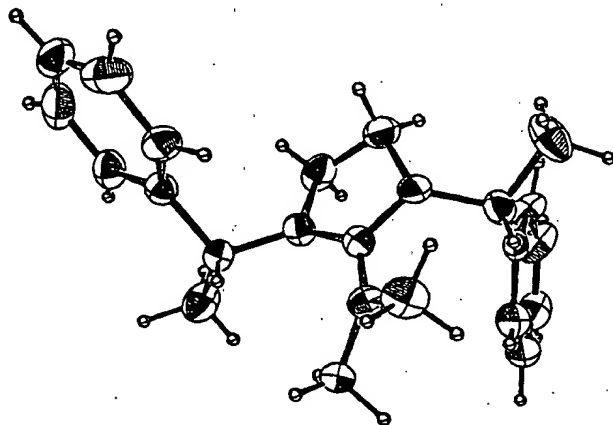


Figure 1.

cessful due to rapid detosylation under the reaction conditions.<sup>12</sup>

However, it was possible to prepare differentially substituted acyclic guanidinium salts by sequentially introducing two different secondary amines (Scheme 2, Table 1). The above procedure had to be modified in order to control the product outcome of the reaction. For two amines of markedly different reactivity, this was achieved by adding 1 equiv of the less reactive amine admixed with 1 equiv of triethylamine to a suspension of the phosgeniminium salt in dichloromethane or chloroform. After complete dissolution, the more reactive amine admixed with an equimolar amount of triethylamine was added to the now *in situ* prepared less electrophilic chloroamidinium intermediate. The desired guanidinium salts were isolated in good to excellent yields.

Guanidinium chlorides 2a–i are hygroscopic and need to be kept under argon at 0 °C. However, these salts can be made more stable by substituting the counterion with PF<sub>6</sub><sup>−</sup> or BF<sub>4</sub><sup>−</sup>. All compounds were fully characterized by the usual spectroscopic data. Compound 2c after counterion exchange with PF<sub>6</sub><sup>−</sup> has been further characterized by X-ray diffraction analysis (Figure 1).<sup>13</sup>

This crystal structure is particularly interesting because the two phenyl groups interact in plane with the guanidinium moiety. This result suggests that the

stacked geometry is more favorable and constitutes a new example of cation-π interactions that are among the many noncovalent forces that contribute to biological structure.<sup>14</sup>

In summary, this paper describes the first convergent one-step synthesis of racemic and chiral guanidinium salts. The key feature of this strategy is the use of highly electrophilic phosgeniminium salts as precursors. It provides direct access to cyclic as well as acyclic guanidinium salts. Moreover, this new strategy has the added advantage of obtaining guanidinium salts derived from three different secondary amines in a one-step reaction.

## Experimental Section

**Materials.** (S)-α-Phenylethylamine was purchased from Aldrich. (1S,2S)-N,N'-Dibenzyl-1,2-cyclohexanediamine,<sup>15</sup> (1S,2S)-N,N'-dimethyl-1,2-cyclohexanediamine,<sup>15</sup> (1S,2S)-N,N'-dimethyl-1,2-diphenyl-1,2-ethanediamine,<sup>15</sup> N-methyl-N-(p-methoxybenzyl)-1(R)-isopropyl-1,2-ethanediamine,<sup>16</sup> N,N-bis(1(S)-phenylethyl)-1,2-ethanediamine,<sup>17</sup> N,N-bis(1(S)-phenylethyl)-1,3-propanediamine,<sup>17</sup> and phosgeniminium salts 1a and 1b<sup>11</sup> were prepared as described in the literature. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in either CDCl<sub>3</sub> or CD<sub>3</sub>OD with a 200 or 300 MHz spectrometer. Melting points could not be measured because guanidinium salts are hygroscopic.

**General Procedure for the Preparation of Cyclic Guanidinium Salts.** To a suspension of 1 equiv of phosgeniminium salt in dry CH<sub>2</sub>Cl<sub>2</sub> (0.3 M) at 0 °C was added dropwise a mixture of 1 equiv of diamine and 2 equiv of triethylamine in CH<sub>2</sub>Cl<sub>2</sub> (0.3 M). After 10 min at 0 °C, stirring was maintained at room temperature until completion of the reaction (complete solubilization of the phosgeniminium salt). The mixture was treated with 15% NaOH and brine. The organic layer was dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure. The residue was then allowed to stand in dry ether overnight. The upper ethereal layer of the resulting biphasic mixture was removed, and the lower phase, containing the guanidinium salt was washed with ether. The guanidinium salt was finally obtained as a solid or as an oil and was stored at 0 °C under an inert atmosphere. Analytically pure compounds were obtained by crystallization or by preparative reverse phase HPLC purification (ZORBAX SB C18, reverse phase). Only compound 2d could not be prepared in a satisfactory state of purity because of partial decomposition on the column or during crystallization.

**N,N,N',N'-Tetramethyl-N,N'-(1(S),2(S)-diphenylethylene)guanidinium Chloride (2a).** Crude compound 2a was obtained as a white solid (100%); analytically pure compound was obtained by preparative HPLC purification; [α]<sub>D</sub><sup>25</sup> = −90.3 (c = 0.034, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) δ 7.47–7.31 (m, 10H), 4.64 (s, 2H), 3.27 (s, 6H), 3.03 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ 165.2, 135.6, 129.4, 127.1, 75.2, 41.5, 36.9; IR (neat) 1642, 1536 cm<sup>−1</sup>; HRMS calcd for C<sub>19</sub>H<sub>24</sub>N<sub>3</sub> (cation) 294.1970, found 294.1964; HPLC (CH<sub>3</sub>OH/H<sub>2</sub>O, 40/60, 0.1% TFA, 1.5 mL/min) t<sub>R</sub> 7 min.

**N,N-Diethyl-N,N'-dimethyl-N,N'-(1(S),2(S)-diphenylethylene)guanidinium Chloride (2b).** Crude compound 2b was obtained as a white solid (90%); analytically pure compound was obtained by preparative HPLC purification; [α]<sub>D</sub><sup>25</sup> = −74.5 (c = 0.07, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) δ 7.50–7.31 (m, 10H), 4.72 (s, 2H), 3.62 (q, J = 7.0 Hz, 4H), 3.00 (s, 6H), 1.39 (t, J = 7.2 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ 165.8, 135.5, 129.4, 127.5, 74.9, 44.4, 36.6, 13.6; IR (neat) 1608, 1547 cm<sup>−1</sup>; HRMS calcd for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub> (cation) 322.2283, found 322.2271; HPLC (CH<sub>3</sub>OH/H<sub>2</sub>O, 40/60, 0.1% TFA, 1.5 mL/min) t<sub>R</sub> 9 min.

(12) Schlama, T.; Gouverneur, V.; Mioskowski, C. Unpublished results.

(13) The authors have deposited atomic coordinates for this structure in the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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***N,N*-Dimethyl-*N,N'*-bis((*S*)- $\alpha$ -phenylethyl)-*N,N'*-ethyleneguanidinium Chloride (2c).** Compound 2c was purified by crystallization ( $\text{C}_6\text{H}_6/\text{CHCl}_3$  1/1) and obtained as a white solid (84%):  $[\alpha]_D^{25} = +50.7$  ( $c = 0.065$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.41–7.23 (m, 10H), 5.10 (q,  $J = 6.9$  Hz, 2H), 3.48 (s, 4H), 3.23 (s, 6H), 1.64 (d,  $J = 7.0$  Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  162.7, 138.1, 128.8, 128.1, 125.7, 55.8, 41.9, 40.8, 17.7; IR (neat) 1609, 1546  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_3$  (cation) 322.2283, found 322.2281. X-ray for compound 2c with  $\text{PF}_6^-$  as counterion: orthorhombic,  $P2_12_12_1$ ,  $a = 8.686$  Å,  $b = 12.252$  Å,  $c = 21.419$  Å,  $V = 2279$  Å<sup>3</sup>,  $Z = 4$ .

***N,N*-Dimethyl-*N,N'*-dibenzyl-1(*S*),2(*S*)-phenyleneguanidinium Chloride (2d).** This compound isolated as a white solid could not be obtained with satisfactory purity after several crystallizations ( $\text{CH}_2\text{Cl}_2/\text{ether}$ ) or HPLC purification: yield: 53%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.37–7.27 (m, 10H),  $\delta_A = 4.98$  and  $\delta_B = 4.59$  (AB system,  $J_{AB} = 17.6$  Hz, 2H), 3.68 (m, 2H), 3.03 (s, 6H), 1.89–0.97 (m, 8H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  167.2, 135.7, 128.9, 127.6, 125.7, 67.6, 51.3, 41.3, 27.8, 23.6; IR (neat) 2941, 1692, 1632  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{23}\text{H}_{30}\text{N}_3$  (cation) 348.2440, found 348.2453.

***N,N*-Dimethyl-*N,N'*-bis((*S*)- $\alpha$ -phenylethyl)-*N,N'*-trimethyleneguanidinium Chloride (2e).** Crude compound 2e was obtained as a white solid (96%); analytically pure compound was obtained by preparative HPLC purification:  $[\alpha]_D^{25} = +196.0$  ( $c = 0.15$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 200 MHz)  $\delta$  7.47–7.33 (m, 10H), 5.17 (q,  $J = 7.1$  Hz, 2H), 3.24 (s, 6H), 3.11 (m, 2H), 2.90 (m, 2H), 1.76 (d,  $J = 7.1$  Hz, 6H), 1.15 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  160.9, 136.9, 128.5, 128.1, 126.1, 76.4, 58.5, 40.4, 39.3, 23.7, 15.4; IR (neat) 1547  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_3$  (cation) 336.2440, found 336.2417; HPLC ( $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ , 40/60, 0.1% TFA, 1.5 mL/min)  $t_R$  14 min.

***N,N*-Dimethyl-*N*-methyl-*N'*-(*p*-methoxybenzyl)-*N,N'*-(1(*R*)-isopropylethylene)guanidinium Chloride (2f).** Crude compound 2f was obtained as a white solid (90%); analytically pure compound could be obtained by preparative HPLC purification or crystallization ( $\text{C}_6\text{H}_6/\text{CHCl}_3$  1/1):  $[\alpha]_D^{25} = +71.6$  ( $c = 0.07$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$  7.26 (d,  $J = 8.6$  Hz, 2H), 6.97 (d,  $J = 8.4$  Hz, 2H), 4.54 ( $\delta_A$ ) and 4.48 ( $\delta_B$ ) (AB system,  $J_{AB} = 15.8$  Hz, 2H), 3.94 (t, 1H), 3.60 (s, 3H), 3.57 (m, 1H), 3.23 (m, 1H), 3.13 (s, 6H), 3.12 (s, 3H), 1.78 (m,  $J = 6.6$  Hz, 1H), 0.88 (d,  $J = 6.8$  Hz, 3H), 0.77 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  163.3, 159.4, 128.5, 125.5, 114.3, 66.9, 55.1, 51.8, 49.1, 47.6, 40.2, 37.2, 30.6, 17.2, 16.1; IR (neat) 1634, 1551  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{17}\text{H}_{28}\text{N}_3\text{O}_1$  (cation) 290.2232,

found 290.2214; HPLC ( $\text{CH}_3\text{OH}/\text{H}_2\text{O}$  50/50, 0.1% TFA, 1.5 mL/min)  $t_R$  10 min.

***N,N*-Dimethyl-*N,N'*-diethyl-*N,N'*-tetramethyleneguanidinium Chloride (2g).** Crude compound 2g was obtained as a colorless oil (90%); analytically pure compound was obtained by preparative HPLC purification: yield 100%;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$  3.44 (m, 4H), 3.29 (q,  $J = 7.0$  Hz, 4H), 2.96 (s, 6H), 2.02 (m, 4H), 1.20 (t,  $J = 7.2$  Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  159.3, 49.4, 45.6, 43.3, 42.0, 40.1, 24.8, 24.3, 12.8; IR (neat) 1573  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{11}\text{H}_{24}\text{N}_3$  (cation) 198.1970, found 198.1966; HPLC ( $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ , 25/75, 0.1% TFA, 1.5 mL/min)  $t_R$  4 min.

***N,N*-Dimethyl-*N,N'*-dibenzyl-*N,N'*-tetramethyleneguanidinium Chloride (2h).** Crude compound 2h was obtained as a white solid (88%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.40–7.15 (m, 10H), 4.04 (br s, 4H), 3.39 (m, 4H), 2.90 (s, 6H), 1.95 (m, 2H), 1.81 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  159.5, 133.9, 129.1, 128.6, 53.7, 49.9, 49.2, 39.9, 24.8, 24.4; IR (neat) 1584, 1537  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_3$  (cation) 322.2283, found 322.2309.

***N,N*-Dimethyl-*N,N'*-diisopropyl-*N,N'*-tetramethyleneguanidinium Chloride (2i).** Crude compound 2i was obtained as a white solid (76%); analytically pure compound was obtained by preparative HPLC purification:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 300 MHz)  $\delta$  3.71 (t,  $J = 7.0$  Hz, 2H), 3.46 (m, 4H), 3.01 (s, 6H), 2.05 (m, 4H), 1.37 (d,  $J = 6.8$  Hz, 12H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  160.4, 51.9, 50.0, 47.8, 46.3, 24.7, 24.1, 22.4; IR (neat) 1578, 1518  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{28}\text{N}_3$  (cation) 226.2283, found 226.2287; HPLC ( $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ , 30/70, 0.1% TFA, 1.5 mL/min)  $t_R$  5 min.

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**Supporting Information Available:**  $^1\text{H}$  NMR spectrum of compounds 2a–i (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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